일반연제

Effect of Rifampin and Itraconazole on the Pharmacokinetics and Pharmacodynamics of Ebastine

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Objectives: Ebastine, a nonsedative H_1 receptor antagonist, is almost completely metabolized to the dealkylated metabolite by a first-pass effect. The conversion of hydroxy metabolite to active metabolite, carebastine, and the generation of desbutyrophenone (Des-BP) are mainly catalyzed by CYP3A4, whereas the oxidation of ebastine to hydroxyebastine is exclusively mediated by CYP2J2. Our objective was to evaluate the effect of itraconazole and rifampin, CYP3A4 inhibitor and inducer, on the pharmacokinetics and pharmacodynamics of ebastine.

Methods: In unblinded 3-way parallel design with a 2-week washout period, 10 healthy subjects were treated with itraconazole for 6 days, rifampin for 10 days, or not. A single oral dose of 20 mg ebastine was administered to subjects and blood to 72 hrs and urine to 24 hrs were collected. Histamine-induced wheal and flare reactions were measured to assess the effects on the antihistamine response to 12 hrs. Ebastine and their metabolites in plasma and urine samples were determined by LC/MS/MS with MRM mode.

Results: Itraconazole pretreatment led to about 3-fold increase in the AUC from 0 to infinity (AUC_{inf}) and Cmax and a decrease to 10~20% in the oral clearance and apparent volume of distribution of ebastine compared with only ebastine dosing. The AUC_{inf} of careabstine was increased by 3-fold. Rifampin reduced significantly AUC_{inf} and Cmax of ebastine and metabolites except for Des-BP. Especially, rifampin decreased AUC_{inf} (from 2651.98 ± 1314.40 to 376.81 ± 216.33ng/ml*hr) and shortened the half-lives (26.46 ± 5.75 to 6.90 ± 1.51 hr) of carebastine. The suppressive effect on histamine-induced wheal and flare reactions after ebastine dosing tended to be higher with itraconazole pretreatment, but statistically not significant, whereas rifampin pretreatment decreased that effect significantly when compared with single dose of ebastine.

Conclusions: Itraconazole and rifampin pretreatment significantly altered the disposition of ebastine and its active metabolite, carebastine, in human. These pharmacokinetic differences resulted in the change of its antihistamine effect.